REMARKS

In the Office Action dated March 10, 2004, claims 22-31 and 33-36, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 22-31 and 33-36 remain in this application, claim 32 has been canceled and new claim 38 has been added to the application.

The office action indicates that claim 37 has been withdrawn from consideration. Applicants contend that claim 37 should be examined because previous claim 32 was canceled in favor of claim 37. Claim 32 recited a second cell and depended from claim 22 which recites the first cell. Claim 32 encompassed a method where the cells were in contact with each other. In view of this, applicants request that claim 37 be examined in the present application.

New claim 38 has been added to the application. The step of disturbing G protein mediated signal transduction was previously recited in claim 22. Therefore, new claim 38 does not raise any new issues.

Claims 22, 24, 26 27, 33, 35 and 36 were objected to due to the informalities discussed on page 3 of the office action. These claims have been amended as suggested in the office action except for claims 22 and 36 where the language "resulting in" has been deleted. In view of these amendments applicants request that these objections be withdrawn.

Claims 22-31, 33, 34 and 36 were rejected under 35 USC §112, first paragraph. The office action contends that "the specification does not adequately describe that G protein coupled receptor initiated extracellular signal pathway recited in claims 22-31, 33, 34 and 36". Applicants respectfully disagree and point out page 17, lines 2-9, of the specification which indicates that in the signal pathway, a ligand activates the G protein by interacting with a G protein coupled receptor which produces an intracellular signal that induces the extracellular activity which results in the processing of a transmembrane growth factor precursor and release of the mature factor which interacts with the receptor leading to autophosphorylation and signal generation. Applicants also point out the examples on pages 10-11 and 11-12 and figures 1a-e and 2a-c which describe a G protein coupled receptor initiated extracellular signal pathway. In view of this disclosure, applicants request that this rejection be withdrawn.

Claims 22-31 and 33-36 were rejected under 35 USC §112, second paragraph, as indefinite. The office action contends that disturbing or stimulating G protein mediated signal transduction in a cell could be the same as contacting the cell with a compound affecting a G protein or G protein coupled receptor. Applicants point out that these are two different steps. Though both steps could result in stimulation of a receptor tyrosine kinase, in the present invention the second step of contacting the cell with a compound affecting a G protein or G protein coupled receptor is carried out on cells which already have a disturbed G

protein mediated signal transduction (resulting from the first step). Thus, claims 22 and 36 are not indefinite.

Claim 35 was rejected as indefinite as no step was recited for identifying compounds for modulating G-protein mediated signal transduction. Claim 35 has been amended to include such a step.

Claim 36 was rejected as it was unclear what protein the extracellular domain was from. Claim 36 has been amended to indicate that the extracellular domain is an EGFR domain.

Claim 36 was also rejected as indefinite as it was unclear whether the "signal transduction pathway" was the same as the "G protein mediated signal transduction pathway". Claim 36 has been amended to indicate that the "signal transduction pathway" is the "G protein mediated signal transduction pathway". In view of the above amendments, applicants request that these rejections be withdrawn.

Claims 22-26, 28-31 and 33-36 were rejected under 35 USC §102(a) over Dong et al. Applicants point out that Dong et al. does not stimulate/disturb the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims. The office action erroneously indicates that Dong et al. contains all of the features required for stimulating a GPCR initiated extracellular signal pathway. For example, the office action contends that by the administration of batimastat and EGF as disclosed by Dong et al. a G protein or GPCR initiated extracellular signal transduction pathway is activated. This is incorrect. Batimastat is an inhibitor of EGFR tyrosine phosphorylation and, thus,

cannot stimulate the G protein/GPCR mediated signal transduction pathway. In addition, as shown in the present application (Fig. 4c), exogenous EGF is not capable of stimulating cleavage of pro-HB-EGF to give HB-EGF and, thus, has no effect on the G protein mediated signal transduction pathway.

Dong et al. teaches that batimastat and the antibody Ab 225 inhibit basal (autocrine) tyrosine phosphorylation of EGFR in HMEC, whereas exogenous EGF activates tyrosine phosphorylation (cf. page 6238, right column and Fig 4). The conclusion in the office action that batimastat plus EGF together increase tyrosine phosphorylation of EGFR is completely wrong. According to Dong et al. batimastat inhibits basal EGFR activity not EGFR activity stimulated by exogenous EGF. Therefore, the addition of both substances leads to increased EGFR activity, whereby the latter is caused only by EGF and thus, has nothing to do with influencing the G protein/GPCR signal transduction pathway. The logic used in the office action is contradictory in itself in that batimastat, on the one hand, blocks EGFR tyrosine phosphorylation, however, on the other hand, together with EGF is used to activate EGFR tyrosine phosphorylation. This means that the feature of stimulation of a G protein or GPCR mediated extracellular signal transduction pathway was not achieved by batimastat alone, by EGF alone nor by batimastat plus EGF and thus, is not disclosed by Dong et al. The two-stage process of the present invention (activating a receptor tyrosine kinase by stimulating/disturbing the G protein/GPCR mediated pathway and modulating the receptor tyrosine kinase activation by contacting the cell with a compound affecting a G protein/GPCR initiated extracellular signal pathway) is

neither explicitly nor inherently disclosed by Dong et al. Dong et al. is not concerned with a G protein or GPCR initiated signal transduction pathway and Dong et al. does not stimulate/disturb the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims. Contrary to statements made in the office action, Dong et al. does not disclose all of the steps in the presently claimed process and thus does not inherently anticipate the presently claimed invention. In view of this, applicants request that this rejection be withdrawn.

Claim 27 was rejected under 35 USC §103 (a) over Dong et al. in view of Miyoshi et al. Miyoshi was cited for the disclosure of a cell line which produces proHB-EGF and contains EGFR. Miyoshi does not suggest or disclose modulating G-protein mediated signal transduction or a step of stimulating/disturbing the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims and thus does not cure the above discussed deficiencies in Dong. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 22-31 and 33-38 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an

extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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